Dipeptidyl-peptidase-4 (DPP-4) Inhibitors: Saxagliptin, Sitagliptin, Linagliptin, Alogliptin Criteria for Use

VA Pharmacy Benefits Management Services, Medical Advisory Panel and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

Saxagliptin is on the VA National Formulary (the other DPP-4-inhibitors remain non-formulary)

Exclusion Criteria

- ❑ History of a serious hypersensitivity reaction to DPP-4 inhibitors such as anaphylaxis or angioedema
- ❑ Patients with a history of acute pancreatitis, chronic or recurring pancreatitis and those with a history of pancreatitis secondary to exenatide or another DPP-4 inhibitor or has pancreatic cancer.**

***It is unknown whether use of these medications in patients with other risk factors for pancreatitis (such as elevated triglycerides, gallstones, alcohol abuse) increases rates of adverse events, but their presence should be considered in the decision to use these agents.*

Inclusion Criteria[1]

Use as monotherapy (must meet both criteria)

- ❑ Candidate for oral therapy and is intolerant of or has contraindications to use of metformin and sulfonylureas
- ❑ Expected change in hemoglobin A1c (A1C) is < 1% in order to reach patient specific goal[2]

Add-on therapy as part of an oral 2 drug regimen (must meet all 3 criteria)

- ❑ Inadequate glycemic control on monotherapy with metformin (at maximally tolerated dose) or sulfonylurea (at 50% maximal dose or highest tolerated dose)
- ❑ Unable to tolerate or has contraindications to addition of a 2nd agent from the above mentioned group
- ❑ Expected change in A1C is < 1% in order to reach patient specific goal[2]

Add-on therapy as part of an oral 3-drug regimen (must meet all 4 criteria)

- ❑ Inadequate glycemic control on combination therapy with sulfonylurea and metformin
- ❑ Patient is not a good candidate for addition of insulin[3]

  OR

  Patient declines insulin despite receiving information on pertinent therapeutic options and on his/her target A1c goal as well as on the ability of the various therapeutic options to achieve the desired A1c target goal and/or meet other clinical needs. Counseling should involve the patient's primary care provider(s) and, when feasible, instruction about and demonstration of insulin injection by those with expertise in diabetes care (e.g., diabetes educators, nurses, or other appropriate clinicians).
- ❑ Expected change in A1C is < 1% in order to reach patient specific goal [2]

Add-on therapy as part of an oral 4-drug regimen

The efficacy and safety of such a combination is not known and should be strongly discouraged. Such a trial might rarely be considered in patients with inadequate glycemic control on 3 drug therapy and who would not be a good candidate for the addition of insulin.

Dosage

Refer to product labeling for dosing information
Please note the following:

- Sitagliptin, saxagliptin, and alogliptin require dosage adjustment for patients with renal impairment
- The dose of saxagliptin requires adjustment if taken concurrently with a strong CYP3A4/5 inhibitor
- Linagliptin should not be used if patient is receiving a P-glycoprotein or CYP3A4 inducer
- When used with a sulfonylurea, a lower dose of the sulfonylurea may be required as hypoglycemia was reported more often in those treated with this combination.

Issues for Consideration

The long-term cardiovascular safety trial for saxagliptin (SAVOR) showed that there was no increase or decrease in the primary endpoint (composite of CV death, nonfatal MI, or nonfatal ischemic stroke). Sensitivity analysis performed by the FDA of the on-treatment population revealed an increased incidence of death in the patients receiving saxagliptin; the significance of this finding is unknown

A secondary endpoint from the SAVOR trial found a higher risk of hospitalization for heart failure in patients receiving saxagliptin relative to placebo HR=1.27 [95%CI 1.07, 1.51; p=0.007]. Hospitalization due to heart failure was not a predefined endpoint In the EXAMINE trial for alogliptin. However, a post hoc analysis found a numerically higher risk of hospitalization for heart failure in patients receiving alogliptin relative to placebo HR=1.19 [95%CI 0.90, 1.58; p=0.220]. It is unclear if risk for heart failure is a class effect among the DPP-4 inhibitors. Results from the long-term cardiovascular safety trials for sitagliptin and linagliptin are needed to better address this issue.

Pancreatitis has been reported with the DPP-4 inhibitors. Monitor patients carefully for the development of pancreatitis after initiation or dose increases of agent. Discontinue agent if pancreatitis is suspected while using these products.

Some infections have been reported more often with DPP-4 inhibitors than placebo: upper respiratory tract infection, urinary tract infection, nasopharyngitis

Serious allergic and hypersensitivity reactions (e.g. anaphylaxis, angioedema, exfoliative skin conditions including Stevens-Johnson syndrome) have been reported with the DPP-4 inhibitors. If these reactions occur, discontinue agent and initiate alternative treatment for diabetes.

Consider discontinuing the DPP4 inhibitor if insulin is initiated.

Discontinuation criteria

Discontinue if little to no improvement in glycemic (e.g., A1C, postprandial glucose) goals are seen after 3-6 months of therapy

[1] Insulin may be considered at any time prior to using a DPP-4 inhibitor; however, it should be considered if patient is symptomatic or a greater reduction beyond what is achievable by a DPP-4 inhibitor is desired.

[2] Refer to the Va/DoD Diabetes Guidelines **http://www.healthquality.va.gov/index.asp** for recommendations on individualizing A1C targets

[3] Type 2 diabetics with special circumstances where the risk of severe hypoglycemia and/or its potential consequences are significant and/or catastrophic (e.g. frail elderly, liver failure, severe renal failure, workers with frequent rotating shifts and occupations such as truck or bus drivers or heavy machinery operators) or patients who are unable to master injection technique.

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